Exhibit G

Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma

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• Encephalopathy, Post-traumatic • Neurodegenerative disorders • Concussion • Athletic injuries • Dementia • Motor neuron disease

It has been understood for decades that certain sporting activities may increase an athlete's risk of developing a neurodegenerative disease later in life. Not surprisingly, this association was originally noted in boxers, athletes who receive numerous blows to the head during training and competition. In 1928, Harrison Martland, a New Jersey pathologist and medical examiner, first described the clinical spectrum of abnormalities found in "nearly one half of the fighters who have stayed in the game long enough."[1]

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Boxers exhibiting cognitive, behavioral, or motor abnormalities were well known to lay persons, sportswriters, and others within the boxing community and were referred to by various terms, such as "punch drunk," "goofy," and "slug-nutty"[2,3]; later, the more formal term *dementia pugilistica* was introduced to lend medical validity to the condition.[4] By the 1970s, a sufficient number of boxers with dementia pugilistica had been studied pathologically to support the conclusion that this form of neurodegeneration was similar to, but distinguishable from, other causes of neurodegenerative disease.[5] As evidence of the clinical and neuropathologic consequences of repeated mild head trauma grew, it became clear that this pattern of neurodegeneration was not restricted to boxers, and the term chronic traumatic encephalopathy (CTE), originally coined by Miller[6] became most widely used.

Over the last several decades, clinical and neuropathologic evidence of CTE has emerged in association with various sports, including American football, professional wrestling, professional hockey, and soccer, as well as other activities associated with repetitive mild head trauma, such as physical abuse, epileptic seizures, and head banging.[7–13] Although the incidence and prevalence of CTE is currently unclear, it probably varies by sport, position, duration of exposure, and age at the time of initial or subsequent head trauma, and with additional variables, such as genetic predisposition. To date, there have been no randomized neuropathologic studies of CTE in deceased athletes, and as such, there is a selection bias in the cases that have come to autopsy. If one considers the prevalence in deceased professional American football players who died between February 2008 and June 2010, there were 321 known player deaths[14] and the brains of 12 of the 321 underwent postmortem neuropathologic examination at Boston University Center for the Study of Traumatic Encephalopathy (BU CSTE). All 12 examined neuropathologically showed evidence of CTE, suggesting an estimated lifetime prevalence of at least 3.7%. If one assumes that all deceased players who did not come to autopsy did not have CTE and that the amount of head trauma in professional football has remained fairly constant over the past 5 decades, a prevalence of 3.7% would result. Although this represents a conservative estimate, it suggests a significant public-health risk for persons who suffer repetitive mild traumatic brain injury (TBI).

CLINICAL SIGNS AND SYMPTOMS OF CTE

Whereas concussion and postconcussion syndrome represent temporary states of neuronal and axonal derangement, CTE is a neurodegenerative disease that occurs years or decades after recovery from the acute or postacute effects of head trauma. The exact relationship between concussion and CTE is not entirely clear, although repetitive axonal perturbation may initiate a series of metabolic, ionic, membrane, and cytoskeletal disturbances, which trigger the pathologic cascade that leads to CTE in susceptible individuals.[15,16] The onset of CTE is often in midlife, usually after athletes have retired from their sport. In some individuals, the early manifestations of CTE affect behavior; in particular, individuals with neuropathologically documented CTE have been described by family and friends as being more irritable, angry, or apathetic or as having a shorter fuse. Increased suicidality seems to be a particularly salient symptom of CTE.[17] In other cases, cognitive difficulties may be the first signs to emerge, with poor episodic memory and executive functioning being two of the most common cognitive dysfunctions reported. Later in the disease, movement (eg, parkinsonism), speech, and ocular abnormalities may emerge in the context of declining cognition and worsening comportment. A minority of cases with neuropathologically documented CTE developed dementia before death; the relative infrequency of

dementia in individuals with CTE may be due in part to many individuals with CTE having committed suicide or died from accidents or drug overdose at an early age.[11,17]

NEUROPATHOLOGY OF CTE

Gross Pathology

Neuropathologic studies of athletes with a history of repeated mild head injuries have produced several consistent findings that, together, make CTE a distinctive disorder. On gross examination, there is often anterior cavum septi pellucidi and, usually, posterior fenestrations. These changes may be caused by the force of the head impact being transmitted through the ventricular system, thereby affecting the integrity of the intervening tissue. Enlargement of the lateral and third ventricles is also commonly seen in CTE; the third ventricle may be disproportionately widened. Additional gross features include atrophy of the frontal and temporal cortices and of the medial temporal lobe, thinning of the hypothalamic floor, shrinkage of the mammillary bodies, pallor of the substantia nigra, and hippocampal sclerosis. Atrophy of the cerebrum, diencephalon, basal ganglia, brainstem, and cerebellum may result in an overall reduction in brain mass.[11]

Microscopic Neuropathology

Tau

Microscopically, CTE is characterized by an abundance of neurofibrillary inclusions in the form of neurofibrillary tangles (NFTs), neuropil threads (NTs), and glial tangles (GTs). The main protein composing NFTs is the microtubule-associated protein tau, and NFTs are aggregates of filamentous tau polymers. Although CTE shares many microscopic similarities with Alzheimer disease (AD) and other tauopathies, it has several distinguishing features. First, the distribution of tau pathology is unique; it is most commonly found in the more superficial cortical laminae (II and III), whereas tau NFTs in AD are preferentially distributed in large projection neurons in layers III and V. Further, the regional tau pathology is extremely irregular, largely confined to uneven foci in the frontal, temporal, and insular cortices, unlike the more uniform cortical NFT distribution seen in AD. Tau NFTs, NTs, and GTs are found throughout the medial temporal lobe, often in densities greater than those found in severe AD, and are also prominent in the diencephalon, basal ganglia, and brainstem. NTs and GTs are also found in the subcortical white matter. Finally, NFTs in CTE are most dense at the depths of cortical sulci, and are typically perivascular, which might indicate that disruptions of the cerebral microvasculature and the blood brain barrier that occur at the time of the traumatic injury play a critical role in the formation of NFTs.[11]

Although the precise pathologic mechanisms that tie repeated mild head injuries to NFT formation are not known, they may involve a series of diffuse axonal injuries (DAI) set in motion by the initial trauma and aggravated by subsequent mild traumatic injuries. During a TBI, the brain and spinal cord undergo shear deformation producing a transient elongation or stretch of axons. Traumatic axonal injury results in alterations in axonal membrane permeability, ionic shifts including massive influx of calcium, and release of caspases and calpains that might trigger tau phosphorylation, misfolding, truncation, and aggregation, as well as breakdown of the cytoskeleton with dissolution of microtubules and neurofilaments.[15,18,19]

Increasing evidence indicates that tau phosphorylation, truncation, aggregation, and polymerization into filaments represents a toxic gain of function, and continued accumulation of tau leads to neurodegeneration. This is supported by tau's involvement in some genetic forms of frontotemporal degeneration[20] and by work that shows

that plasmids containing human tau complementary DNA constructs microinjected into lamprey neurons in situ produce tau filaments that accumulate and lead to neuronal degeneration.[21,22] However, it is also possible that the intracellular NFTs, by themselves, are the byproducts rather than the cause of cellular injury and that NFT formation indicates neurons that survived the initial injury and sequestered the abnormally phosphorylated, truncated, and folded tau.[23] A possible tau toxic factor or transcellular propagation by the misfolded tau protein may explain how a neurodegeneration that starts multifocally around small blood vessels or in the depths of cortical sulci ultimately spreads to involve large regions of brain as a systemic degeneration, such as CTE.[24]

Beta-amyloid

Beta-amyloid (Aβ) deposits are found in 40% to 45% of individuals with CTE, in contrast to the extensive Aβ deposits that characterize nearly all cases of AD. Although neuritic plaques are typically abundant in AD and are essential to the diagnosis, Aβ plaques in CTE, when they occur, are less dense and predominantly diffuse.[11] Despite the fairly minor role Aβ plaques seem to play in the neuropathologic manifestation of CTE, the role of Aβ in the pathogenesis of CTE has yet to be elucidated. It is known that acute head injuries cause an upregulation of amyloid precursor protein (APP) production and that Aβ plaques may be found in up to 30% of patients who die within hours of TBI.[25–27] DAI, often a consequence of mild TBI, is thought to influence changes in Aβ after head injury. Interruption of axonal transport causes an accumulation of multiple proteins in the axon, including APP, in varicosities along the length of the axon or at disconnected axon terminals, termed axonal bulbs.[28] Although the axonal pathology in TBI is diffuse in that it affects widespread regions of the brain, typically, the axonal swellings are found in multifocal regions of the subcortical and deep white matter, including the brainstem. Because of the rapid and abundant accumulation of APP in damaged axons after TBI, APP immunostaining is used for the pathologic assessment of DAI in humans. Accordingly, this large reservoir of APP in injured axons might be aberrantly cleaved to rapidly form Aβ after TBI.[25,29,30] However, it remains unclear whether the large quantities of APP and Aβ found in damaged axons after TBI play any mechanistic role in neurodegeneration or neuroprotection.[28,31,32] Moreover, it is unknown how long the increased APP and Aβ lasts or what mechanisms may result in variable clearance.

TDP-43

Recently, in addition to severe tau neurofibrillary pathology, the authors found a widespread TDP-43 proteinopathy in more than 80% of their cases of CTE.[13] Moreover, in 3 athletes with CTE who developed a progressive motor neuron disease several years before death, there were extensive TDP-43 immunoreactive inclusions in the anterior horns of the spinal cord, along with tau-immunoreactive GTs, neurites, and, occasionally, extensive NFTs. These findings suggest that a distinctive, widespread TDP-43 proteinopathy is also associated with CTE and that, in some individuals, the TDP-43 proteinopathy extends to involve the spinal cord and is clinically manifest as motor neuron disease with a presentation that may appear similar to amyotrophic lateral sclerosis (ALS).[13] The shared presence of 2 aggregated phosphorylated proteins associated with neurodegeneration in the great majority of cases of CTE suggests that a common stimulus, such as repetitive axonal injury, provokes the pathologic accumulation of both proteins.[33] Recent studies in vitro and in vivo suggest that overexpression of wild-type human TDP-43 and its dislocation from the neuronal nucleus to the cytoplasm are associated with neurodegeneration and cell death.[34–36] By virtue

of its capacity to bind to neurofilament messenger RNA (mRNA) and stabilize the mRNA transcript, TDP-43 plays a critical role in mediating the response of the neuronal cytoskeleton to axonal injury. TDP-43 is intrinsically prone to aggregation, and its expression is upregulated after experimental axotomy in spinal motor neurons of the mouse.[37] Traumatic axonal injury may also accelerate TDP-43 accumulation, aggregation, and dislocation to the cytoplasm, thereby enhancing its neurotoxicity.

CLINICAL IMPLICATIONS

CTE is a Potential Late Effect of Repeated Head Injuries

CTE is not thought to be a long-term sequela after a specific head trauma. Rather, its clinical symptoms emerge later in life, usually after athletes retire from their sport. Like most other neurodegenerative diseases that cause dementia, CTE has an insidious onset and gradual course. Based on a recent review of neuropathologically confirmed CTE in athletes[11], the mean age at onset is 42.8 years (SD = 12.7; range = 25–76 years). On average, onset occurs approximately 8 years after retirement (SD = 10.7), although approximately one-third of athletes were reportedly symptomatic at the time of retirement. In athletes, the course seems to be considerably protracted (mean duration = 17.5 years, SD = 12.1), especially in boxers. The average duration of the disease in boxers is 20 years (SD = 11.7) and 6 years in American football players (SD = 2.9).[11] If the affected individual does not die of other causes, full-blown clinical dementia may occur late in the course of the disease.

Diagnosis of CTE

Currently, the clinical diagnosis of CTE is difficult because there are no consensus diagnostic criteria or large-scale longitudinal clinicopathologic correlation studies. The differential diagnosis of CTE often includes AD[38] and frontotemporal dementia (FTD)[39], depending on the age at onset and the presenting problem. Older individuals with memory difficulties may seem to have AD, and, in fact, may have evidence of AD and CTE neuropathologically.[11] When the age at onset is earlier (eg, 40s or 50s) and the patient presents with behavioral dysregulation or apathy, it may be difficult to rule out FTD. Although a history of remote head trauma may be suggestive of CTE, head trauma has been implicated as a risk factor of AD, Parkinson disease, ALS, and other neurodegenerative diseases.[40–42] Therefore, without neuropathologic confirmation, currently, a clinical diagnosis of CTE cannot be made with a high degree of confidence. Furthermore, the clinical phenotype of CTE may be confounded by alcohol or other drug abuse. Several individuals with neuropathologically confirmed CTE are thought to have developed problems with drug abuse as a consequence of the loss of inhibitory control caused by the neurodegenerative disease. From a clinical perspective, however, it can be difficult to determine whether the drug abuse problems are a cause of symptoms or simply one of many ways in which CTE is manifested.

Although the neuropathologic features of CTE seem to be distinct from other neurodegenerative diseases, no currently agreed neuropathologic criteria exist for the diagnosis of CTE. Once established, these criteria can be applied at autopsy in large-scale, prospective longitudinal studies of athletes with a history of repetitive head injuries. Establishing neuropathologic diagnostic criteria would allow for the identification of clinical criteria and biomarkers to improve the accuracy of CTE diagnosis in the living.

Several biomarkers are believed to have the potential to contribute to identifying CTE in vivo. For instance, the changes to white-matter integrity caused by repeated head trauma may be amenable to detection using diffusion tensor magnetic resonance imaging.[43] Magnetic resonance spectroscopy may be capable of detecting changes

in glutamate/glutamine, N-acetyl aspartate, and myo-inositol, molecular abnormalities that may serve as markers of brain damage caused by head injuries.[44] Further, measuring tau and phospho-tau in cerebrospinal fluid may yield diagnostically useful markers of CTE.[45]

Risk and Protective Factors

CTE research is in its infancy, and decades of research are probably necessary to achieve CTE diagnosis early in its course using a combination of clinical tools and biomarkers. However, the research already conducted has profound implications for current practice by medical professionals, athletic trainers, and related specialists, as well as policy makers in government and athletic organizations. CTE is the only known neurodegenerative dementia with a specific identifiable cause; in this case, head trauma. It is unknown whether a single blow to the head is sufficient to initiate the metabolic cascade that precedes the clinical and neuropathologic changes characteristic of CTE, because all confirmed cases of CTE to date have had a history of multiple head injuries. Therefore, the most obvious way to prevent CTE is, in theory, to prevent repetitive head injuries from occurring. In some sports, such as boxing and American football, it may be impossible to prevent repetitive head injuries, especially the repeated subconcussive blows that are characteristic of the impacts felt by offensive and defensive linemen in football on nearly every play. For sports in which repeated blows to the head are unavoidable, proper concussion assessment and management may be paramount for preventing long-term consequences. Currently, it is unknown whether returning to play while symptomatic from a previous concussion or sustaining a second concussion while symptomatic is a risk factor of developing CTE. However, other strategies to reduce the number and severity of head traumas are possible, such as limiting full-contact practices, implementing rules of play that diminish the likelihood of repeated head trauma (eg, removing the 3-point stance in football), or increasing the use of newer protective headgear aimed at absorbing force, thus diminishing the impact to the brain.

Along these lines, many potential variables surrounding head trauma in athletes may be important for preventing CTE later in life. The sport played and the position played within each sport may be relevant; for instance, boxers receive a greater proportion of rotational forces to the head, whereas American football players receive a greater proportion of linear forces to the head.[46] Even within the same sport, athlete exposure to head injuries can differ considerably. In American football, some positions, such as wide receiver, may receive occasional severe blows with the potential to cause unconsciousness, whereas other players, such as linemen, may take hundreds of small impacts per season, most of which are not, by themselves, forceful enough to cause symptoms.[47] It is unknown whether CTE is more likely to occur after a small number of severe head injuries, a large number of subconcussive injuries, or other forms of head trauma. Currently, investigations are ongoing that attempt to quantify the force of head impacts across different sports and positions.[48] These findings will play an important role in understanding the specific head injury variables that influence CTE risk.

The age at which athletes suffer their head injuries may also influence CTE risk. At younger ages, the brain may be more vulnerable to injury.[49] Conversely, the increased plasticity of the young brain may be better able to compensate for specific difficulties, such as behavioral dysfunction.[50] It is also not clear whether particular lifestyle factors may be protective against CTE in the context of repetitive head injuries. In other neurodegenerative diseases such as AD, the neuropathology is thought to precede the clinical symptoms, possibly by several decades.[51] The same may be true of CTE, as

evidenced by the presence of CTE neuropathology in asymptomatic individuals studied at autopsy. Conceivably, health and medical factors that are absent or present during this preclinical stage may influence the extent of neurodegeneration or the brain's ability to compensate for any neurodegeneration. For instance, the presence of chronic inflammation, as in that which accompanies medical conditions such as obesity, hypertension, diabetes mellitus, atherosclerosis, and heart disease, may facilitate neurodegeneration and NFT formation.[52–55] Also, as with other neurodegenerative diseases like AD, some individuals may have greater *cognitive reserve*, thus increasing the threshold for the clinical manifestation of the underlying neuropathologic condition.

Genetic variations may also play an important role in moderating the relationships between head trauma, neuropathologic changes, and disordered cognition and behavior. One of the genes thought to influence CTE risk is the apolipoprotein E (APOE) gene. The APOE ε4 allele, important in the genetics of AD, may also increase the risk of CTE. Based on genetic testing conducted in conjunction with neuropathologic examinations of individuals with a history of repeated head injuries, approximately 57% of individuals with neuropathologically confirmed CTE possessed at least one APOE ε4 allele. When contrasted with the estimated 28% of the population possessing at least one APOE ε4 allele,[56] the frequency of this allele in those with CTE seems higher than expected. This genetic link is currently speculative, because formal epidemiologic studies have yet to be conducted. However, individuals carrying the APOE ε4 allele may be more likely to have a poor outcome after TBI, especially in individuals younger than 15 years.[57–59] Epidemiologic data have also implicated the APOE ε4 genotype as a risk factor for the development of AD after TBI,[60,61] and carriers of the APOE ε4 allele were found to be at increased risk of Aβ deposition after TBI.[62]

SUMMARY

CTE is a neurodegenerative disease that occurs later in the lives of some individuals with a history of repeated head trauma. The exact relationship between repetitive mild TBI, with or without symptomatic concussion, and CTE is not entirely clear, although it is possible that repetitive axonal injury sets up a series of metabolic, ionic, and cytoskeletal disturbances that trigger a pathologic cascade, leading to CTE in susceptible individuals. CTE has been reported in association with American football, professional wrestling, soccer, and hockey, as well as in association with physical abuse, epilepsy, and head banging behaviors, suggesting that mild TBI of diverse origin is capable of instigating CTE. CTE often manifests in midlife and produces clinical symptoms of disordered cognition, memory loss and executive dysfunction, depression, apathy, disinhibition, and irritability, as well as parkinsonian signs. The characteristic neuropathologic features of CTE include extensive tau-immunoreactive inclusions scattered throughout the cerebral cortex in a patchy, superficial distribution, with focal epicenters at the depths of sulci and around the cerebral vasculature and widespread TDP-43-immunoreactive inclusions that may occasionally be associated with symptoms of motor neuron disease. Currently, neuropathologic examination of brain tissue is the only way to diagnose CTE, although intense research efforts are underway to identify biomarkers to detect the disease and monitor its progression and to develop therapies to slow or reverse its course. Longitudinal research efforts are underway to shed additional light on the specific variables related to head trauma, neuropathology, and clinical presentation of CTE that remain in question.

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